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PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 667052CMOB	FOR FURTHER ACTION	See Form PCT/IPEA/416
International application No. PCT/AU2005/000590	International filing date *(day/month/year)* 26 April 2005	Priority date *(day/month/year)* 23 April 2004
International Patent Classification (IPC) or national classification and IPC Int. Cl. *A61K 31/195* (2006.01) *A61K 31/138* (2006.01) *A61K 31/137* (2006.01) *A61P 9/04* (2006.01)		
Applicant NORTHERN SYDNEY AND CENTRAL COAST AREA HEALTH SERVICE et al		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 3 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. [X] *(sent to the applicant and to the International Bureau)* a total of 7 sheets, as follows:
      - [ ] sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      - [ ] sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.

   b. [ ] *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or table related thereto, in electronic form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).
4. This report contains indications relating to the following items:

[X]	Box No. I	Basis of the report
[ ]	Box No. II	Priority
[ ]	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
[ ]	Box No. IV	Lack of unity of invention
[X]	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
[ ]	Box No. VI	Certain documents cited
[ ]	Box No. VII	Certain defects in the international application
[ ]	Box No. VIII	Certain observations on the international application

Date of submission of the demand 23 February 2006	Date of completion of this report 10 July 2006
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INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/AU2005/000590

Box No. I Basis of the report

1. With regard to the language, this report is based on:

[X] The international application in the language in which it was filed

[ ] A translation of the international application into , which is the language of a translation furnished for the purposes of:

- [ ] international search (under Rules 12.3(a) and 23.1 (b))
- [ ] publication of the international application (under Rule 12.4(a))
- [ ] international preliminary examination (Rules 55.2(a) and/or 55.3(a))

2. With regard to the elements of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

[ ] the international application as originally filed/furnished

[X] the description:

pages **1-3, 5-13 and 15-31** as originally filed/furnished
pages* **4, 14, 14a and 14b** received by this Authority on **29 May 2006** with the letter of **29 May 2006**
pages* received by this Authority on with the letter of

[X] the claims:

pages as originally filed/furnished
pages* as amended (together with any statement) under Article 19
pages* **32-34** received by this Authority on **29 May 2006** with the letter of **29 May 2006**
pages* received by this Authority on with the letter of

[X] the drawings:

pages **1/6-6/6** as originally filed/furnished
pages* received by this Authority on with the letter of
pages* received by this Authority on with the letter of

[ ] a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing.

3. [ ] The amendments have resulted in the cancellation of:

- [ ] the description, pages
- [ ] the claims, Nos.
- [ ] the drawings, sheets/figs
- [ ] the sequence listing *(specify)*:
- [ ] any table(s) related to the sequence listing *(specify)*:

4. [ ] This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

- [ ] the description, pages
- [ ] the claims, Nos.
- [ ] the drawings, sheets/figs
- [ ] the sequence listing *(specify)*:
- [ ] any table(s) related to the sequence listing *(specify)*:

* *If item 4 applies, some or all of those sheets may be marked "superseded."*

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
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Box No. V **Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)	Claims	1-25	YES
	Claims		NO
Inventive step (IS)	Claims	1-25	YES
	Claims		NO
Industrial applicability (IA)	Claims	1-25	YES
	Claims		NO

2. Citations and explanations (Rule 70.7)

CITATIONS:

D1: ***Cardiovascular Research 49 (2001), Pg. 361-370***

D2: ***Br J clin Pharmac 37 (1994), Pg. 363-369***

D3: ***Current problems in cardiology, Vol. 24 (7), (1999 Jul), Pg. 421-60***

D4: EP 1145 717 A

D5: WO 2001/007025

EXPLANATION:

D1 discloses that clinical trials with aryloxypropanolamine carvedilol show that carvedilol is effective in the reduction of sudden cardiac death due to malignant arrhythmias and decreased the risk of moderate to severe heart failure.

D2 is directed to the evaluation of the cardiac effect of β3-adrenoceptor agonist BRL35135 in man. This document discloses administration of β3-adrenoceptor agonist BRL35135 with β1 and β2 blocker nadolol in human males .

D3 discloses that β-blockers such as CPG 20712A improve survival and enhance left ventricular function in patients with congestive heart failure.

D4 discloses using β-agonists BRL 35135, BRL37344 and compounds CL 316,243 & ICID7114 in the treatment of diabetic cardiomyopathy.

D5 discloses modulation of trachycardia by compound CPG 12177.

Amended claims 1-25 filed on 29 May 2006 are both novel and inventive in light of the disclosure of D1, D2, D3, D4 or D5.

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Summary of the Invention

The present invention aims to provide improved methods for the treatment of conditions characterised by abnormalities of myocardial cell ion levels, in particular abnormalities of cellular Na^+, K^+ or Ca^{2+} ions and so to substantially alleviate deficiencies of current treatments for such conditions. In a particular embodiment the present invention aims to provide improved methods for the treatment of heart failure and myocardial hypertrophy and so to substantially alleviate deficiencies of current treatments.

The present invention is based on the surprising discovery by the inventors that a myocardial cell surface receptor, the β_3 adrenoceptor, activates the membrane Na^+-K^+ pump and is associated with extrusion of Na^+ from myocardial cells.

Accordingly, in a first embodiment of the present invention there is provided a method for the treatment of an individual having a condition characterised by abnormal myocardial cell Na^+, K^+ or Ca^{2+} ion levels, said method comprising administering a therapeutically effective amount of one or more β_3 adrenoceptor agonists to said individual.

In a specific aspect the condition is selected from the group consisting of heart failure and/or myocardial hypertrophy.

According to a second embodiment of the invention there is provided a method for the treatment of an individual suffering from or susceptible to heart failure or myocardial hypertrophy, said method comprising administering a therapeutically effective amount of one or more β_3 adrenoceptor agonists to said individual.

In a specific aspect of the invention the individual is an individual suffering from one or more clinical symptoms of heart failure or myocardial hypertrophy.

In a specific aspect of the invention the β_3 adrenoceptor agonist is selected from the β_3 adrenoceptor agonist groups arylethanolamines, aryloxypropanolamines, trimetoquinols.

In a specific aspect of the invention the β_3 adrenoceptor agonist may be selected from the group consisting of BRL37344, BRL 35135, BRL 26830, BRL 26830A, BRL 35113, ZD7114, ZD 2076, CGP12177, CGP 12177A, CGP-20712A, CL316243, ICI D 7114, ICI215001, ICI 201651, BRL35135A, BRL28410, N-5984, (R)-N-[4-[2-[[2-Hydroxy-2-(pyridin-3-yl)ethyl]amino]ethyl]phenyl]-4-[4-(4-trifluoro-methylphenyl)thiazol-2-yl]benzenesulfonamide (L-796568), (R)-N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)- ethyl]amino]ethyl]phenyl]-1-(4-octylthiazol-2-yl)-5-indolinesulfonamide (L-755507), L-770,644, L-766,892, L-757,793, L-796568, LY-377604, Ro 40-2148, Ro

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trimetoquinols including, but not limited to, BRL37344, BRL 35135, BRL 26830, BRL 26830A, BRL 35113, ZD7114, ZD2076, CGP12177, CGP 12177A, CGP-20712A, CL316243, ICI D 7114, ICI215001, ICI 201651, BRL35135A, BRL28410, N-5984, (R)-N-[4-[2-[[2-Hydroxy-2-(pyridin-3-yl)ethyl]amino]ethyl]phenyl]- 4-[4-(4-trifluoromethylphenyl)thiazol-2-yl]benzenesulfonamide (L-796568), (R)-N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)- ethyl]amino]ethyl]phenyl]-1-(4-octylthiazol-2-yl)-5-indolinesulfonamide (L-755507), L-770,644, L-766,892, L-757,793, L-796568, LY-377604, Ro 40-2148, Ro 16-8714, SB-220646, SB-226552, SB-251023, SB-262552, SR 58306, SR 58375, SR 58339, SR 58611, SR 58611A, SR 59119A, GR-265261-X, AD-9677, 6-[2-(R)-[[2-(R)-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]-2,3-dihydro-1, 4-benzodioxine-2-(R)-carboxylic acid (Yanagisawa *et al* 2000), salbutamol, isoproterenol, tetradydroisoquinoline compounds as described in US Patent No: 6,596,734 to Feller and Miller entitled "Tetradydroisoquinoline compounds for use as β_3 adrenoceptor agonists" and other β_3 adrenoceptor agonists known in the art, for example as described in US Patent No. 6,566,377 to Day and Lafontaine entitled "β_3 adrenergic receptor agonists and uses thereof", US Patent No. 6,696,486 to Bahl entitled "Medical use for atypical β-adrenoceptor agonists", US Patent No. 6,593,341 to Feller and Miller entitled "Beta 3-adrenoceptor agonists, agonist compositions and methods of making and using the same", International Patent Application No. PCT/US00/33222 entitled "Beta-3 adrenoceptor agonists" published as WO 01/42217, and agonists described in Harada *et al* (*Bioorg. Med. Chem. Lett.* 2003, 13(7):1301-1305) entitled "Novel and potent human and rat beta3-adrenergic receptor agonists containing substituted 3-indolylalkylamines", such as those of the series 2-(3-indolyl) alkylamino-1-(3-chlorophenyl)ethanols, for example AJ9677, and agonists included in *The Merck Index*, (13th Edition, Merck & Co., Whitehouse Station, N.J., USA). Additionally, β3 agonists described in Weyer, C., *et al.*, (*Diabetes Metab.* 1999, 25:11), Souza, J., *et al.*, (*Curr. Pharm. Des.* 2001, 7:1433), Weber, A. (*Annu. Rep. Med. Chem.* 1998, 33:193), Cantello, B. and Smith, S. (*Drugs Future* 1991, 16:797), Bloom, J. and Claus, T. (*Drugs Future* 1994, 19:23), Cecchi, R., *et al.*, (*Eur. J. Med. Chem.* 1994, 29:259), are also contemplated in the invention.

It will be appreciated that the method of the invention contemplates the use of any suitable β_3 adrenoceptor agonist and that specific groups and compounds are stated herein by way of exemplification and not by way of limitation.

It will be appreciated that reference to the agents includes all salt (acid or base salt) and hydrates, polymorphs, etc, forms of those agents.

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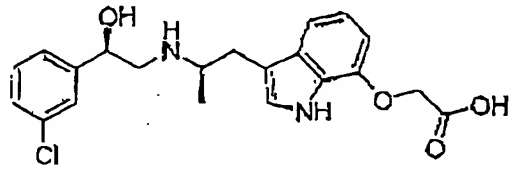
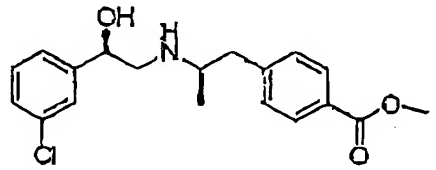
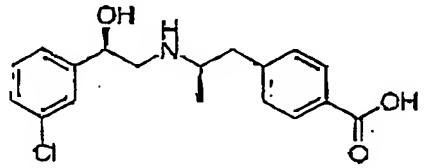
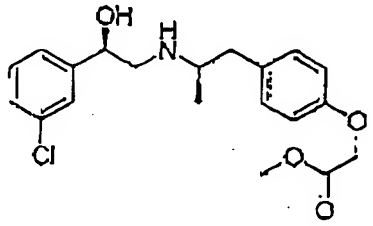
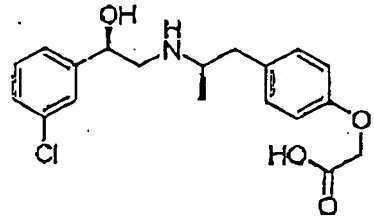
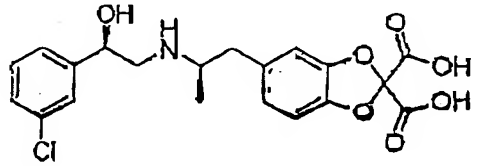
By way of non-limiting example, Table 1 provides illustrative structures of numbers of the β_3 adrenoceptor agonists contemplated by the present invention.

Table 1

AJ-9677	
BRL-26830	
BRL-28410	
BRL-35135	
BRL-37344	
CL-316243	

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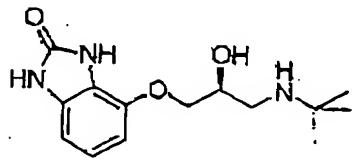
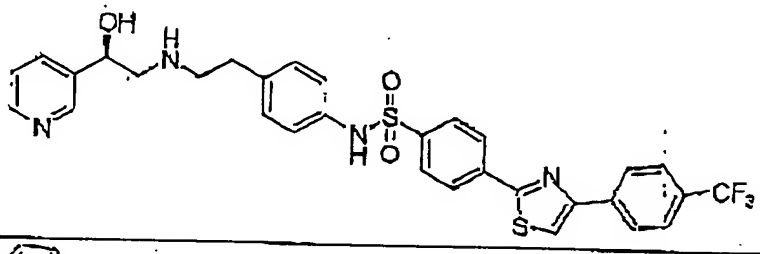
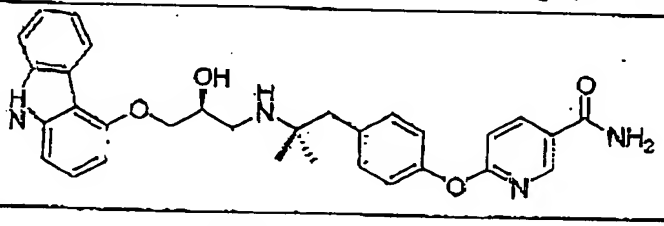
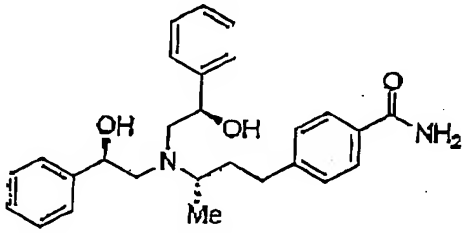
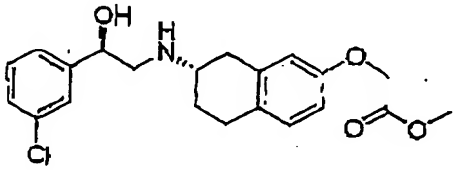
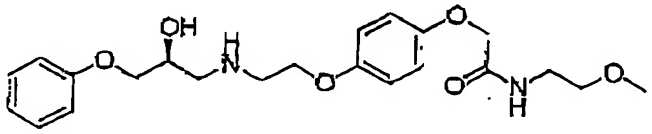
CGP-12177	
L-796568	
LY-377604	
Ro 40-2148	
SR-58611A	
ZD-7114	

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Claims

1. A method for the treatment of an individual having a condition characterised by abnormal myocardial cell Na^+, K^+ or Ca^{2+} ion levels, said method comprising administering a therapeutically effective amount of one or more β_3 adrenoceptor agonists to said individual.

2. The method according to claim 1 wherein the condition is selected from the group consisting of heart failure, and myocardial hypertrophy.

3. A method for the treatment of an individual suffering from or susceptible to heart failure or myocardial hypertrophy, said method comprising administering a therapeutically effective amount of one or more β_3 adrenoceptor agonists to said individual.

4. The method according to claim 3 wherein the individual is an individual having one or more clinical symptoms of heart failure or myocardial hypertrophy.

5. The method according to claim 3 wherein the β_3 adrenoceptor agonist is selected from the group consisting of arylethanolamines, aryloxypropanolamines, trimetoquinols.

6. The method according to claim 3 wherein the β_3 adrenoceptor agonist is selected from the group consisting of BRL37344, BRL 35135, BRL 26830, BRL 26830A, BRL 35113, ZD7114, CGP12177, CGP 12177A, CGP-20712A, CL316243, ICID7114, ICI215001, ICI 201651, BRL35135A, BRL28410, N-5984, (R)-N-[4-[2-[[2-Hydroxy-2-(pyridin-3-yl)ethyl]amino]ethyl]phenyl]-4-[4-(4-trifluoro-methylphenyl)thiazol-2-yl]benzenesulfonamide (L-796568), (R)-N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)-ethyl]amino]ethyl]phenyl]-1-(4-octylthiazol-2-yl)-5-indolinesulfonamide (L-755507), L-770,644, L-766,892, L-757,793, L-796568, LY-377604, Ro 40-2148, SB-220646, SB-226552, SB-251023, SB-262552, SR 58306, SR 58375, SR 58339, SR 58611, SR 58611A, SR 59119A, GR-265261-X, AJ-9677, and agonists of the series 2-(3-indolyl) alkylamino-1-(3-chlorophenyl)ethanols.

7. The method according to claim 3 wherein the β_3 adrenoceptor agonist is BRL37344.

8. The method according to claim 3 wherein the β_3 adrenoceptor agonist further comprises β_1 antagonist activity and or further comprises β_2 antagonist activity.

9. The method according to claim 3 further comprising administering one or more β blockers to said individual.

10. The method according to claim 9 wherein the β blocker is nadolol.

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11. The method according to claim 9 wherein the β blocker is a β_1 and/or β_2 adrenoceptor antagonist.

12. The method according to claim 9 wherein the β blocker is administered to said individual prior to, simultaneously with or subsequent to administration of the one or more β_3 adrenoceptor agonists.

13. The method according to claim 3 further comprising at least partially stabilizing said individual prior to administration of said β_3 adrenoceptor agonist.

14. The method according to claim 13 wherein said stabilizing comprises treatment with one or more compounds selected from the group consisting of ACE-inhibitors, aldosterone antagonists and β adrenoceptor antagonists.

15. A method for treatment of a condition characterised by abnormally high myocardial cell Na^+ ion level, said method comprising administration to an individual having said condition of a therapeutically effective amount of one or more β_3 adrenoceptor agonists.

16. The method according to claim 15 wherein said condition characterised by abnormally high myocardial cell Na^+ ion level is selected from the group consisting of heart failure, myocardial hypertrophy, and diabetic cardiomyopathy.

17. Use of one or more β_3 adrenoceptor agonists for the manufacture of a medicament for treatment of an individual having a condition characterised by abnormal myocardial cell Na^+, K^+ or Ca^{2+} ion levels.

18. One or more β_3 adrenoceptor agonists when used in the treatment of an individual having a condition characterised by abnormal myocardial cell Na^+, K^+ or Ca^{2+} ion levels.

19. Use of one or more β_3 adrenoceptor agonists for the manufacture of a medicament for treatment of an individual suffering from or susceptible to heart failure or myocardial hypertrophy.

20. One or more β_3 adrenoceptor agonists when used in the treatment of an individual suffering from or susceptible to heart failure or myocardial hypertrophy.

21. A pharmaceutical composition when used in the treatment of an individual having a condition characterised by abnormal myocardial cell Na^+, K^+ or Ca^{2+} ion levels, the composition comprising one or more β_3 adrenoceptor agonists together with one or more pharmaceutically acceptable adjuvants, excipients and/or carriers.

22. A pharmaceutical composition when used in the treatment of an individual suffering from or susceptible to heart failure or myocardial hypertrophy, the composition

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comprising one or more β_3 adrenoceptor agonists together with one or more pharmaceutically acceptable adjuvants, excipients and/or carriers.

23. A pharmaceutical composition comprising one or more β_3 adrenoceptor agonists and one or more β_1 and/or β_2 adrenoceptor antagonists, together with one or more pharmaceutically acceptable adjuvants, excipients and/or carriers when used in the treatment of an individual suffering from or susceptible to heart failure or myocardial hypertrophy.

24. A method for the extrusion of Na^+ from a myocardial cell or cells, the method comprising contacting said cell(s) with one or more β_3 adrenoceptor agonist(s).

25. The method according to claim 24 wherein said method comprises Na,K pump stimulation.